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(21) International Application Number: PCT/AU93/00354 (22) International Filing Date: 15 July 1993 (15.07.93) (30) Priority data: PL 3568 17 July 1992 (17.07.92) AU (71) Applicant (for all designated States except US): GLYZINC PHARMACEUTICALS LIMITED [AU/AU]; c/o Bowman Manser & Assoc. Pty. Ltd., 422 King William Street, Adelaide, S.A. 5000 (AU). (72) Inventor; and (75) Inventor/Applicant (for US only): TAYLOR, Reginald, Morton [AU/AU]; 48 Denning Street, Hawthorn, S.A. 5062 (AU). (74) Agent: COLLISON & CO.; 117 King William Street, Adelaide, S.A. 5000 (AU).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: TREATMENT OF SKIN DISEASES (57) Abstract A method of prophylactic or therapeutic treatment of a human or animal body by application of a pharmaceutically acceptable amount by oral, parenteral or topical application of zinc glycerolate for the treatment of skin diseases such as acne and eczema. The application of zinc glycerolate may be as a dry powder, as a cream or ointment or applied topically by an applicator.		

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TREATMENT OF SKIN DISEASES

This invention relates to a zinc glycerol complex when used for the treatment of particular skin diseases of the human or animal body .

BACKGROUND OF THE INVENTION

- 5 The preparation of compounds of glycerol with the transition metals has been described in "*Crystalline cobalt, zinc, manganese and iron alkoxides of glycerol*" by E. W. Radoslovich, M. Raupach, P. G. Slade and R. M. Taylor in Australian Journal of Chemistry 23, 1963 - 1970, (1970). These compounds form during the heating of particular metal oxides, hydroxides or salts with glycerol at
- 10 temperatures around 120° C or higher. In particular the compound with zinc is of interest. The compound of zinc with glycerol is Zinc (1,2,3 - Propanetriolato [2-] - O₁, O₂) homopolymer, stereoisomer and may be termed zinc monoglycerolate, glycerato-zinc, zinc glycerolate and by its trade mark "Glyzinc". The term zinc glycerolate will be used in this specification.
- 15 The compound is described for instance in P.C.T. International Publication WO82/01867 in the names of Taylor and Brock, and comprises a specific product of a reaction between certain zinc compounds and glycerol at certain temperature ranges. The compound is described as having uses in the therapeutic or prophylactic treatment of certain disorders of the human or
- 20 animal skin. It is suggested that the compound may have cosmetic uses and is suggested for the compounding of shaving cream and as a topical application for the prevention of sunburn.

In WO82/01867 zinc glycerolate is mentioned as having a number of prophylactic and therapeutic uses. Thus it is mentioned as being effective in the

25 treatment and prevention of ammoniacal dermatitis (burns in the genital area of babies which originate from ammonia liberated during the decomposition of urine - nappy rash), in the treatment of pruritus, especially in people confined to bed or immobility, for the alleviation of psoriasis, for the treatment and prevention of fungal or bacteriological decomposition of tissue and the resultant

30 odours arising in such complaints as tinea pedis and for the prevention of industrial dermatitis arising from particular environments.

Reference is also made to P.C.T. International Application WO87/01281 in the name of the present applicant, which unlike the first referred to P.C.T. application refers to the use of the zinc glycerolate as a per oral treatment for

gastric bleeding or ulceration or in a topical application as a depot for the slow release of the compound and refers to diffusion through the skin for the treatment of arthritis and zinc insufficiency and includes psoriasis, and refers also to tests against various organisms including fungi, but does not suggest effects in the diseases set out in this specification nor does it suggest prophylactic treatments which it has now been found to have.

The results in the present invention are as quite unexpected as were the first referred to in the publication of Taylor and Brock which does not include reference to these skin diseases for which it has now found to be useful but was directed to skin ailments such as sunburn and it is surprising that it can act for instance on diseases or conditions such as those now found.

BRIEF DESCRIPTION OF THE INVENTION

The skin diseases to which the present invention is directed are acne and eczema.

Common acne or more particularly Acne Vulgaris is the most common of skin conditions. It affects the face, shoulders, back and chest. Acne is caused by the blocking of the channel through which sebum liberated from the sebaceous gland passes to the skin surface. This blocking results in an inflammatory condition of the underlying sebaceous glands.

Other forms of acne such as Acne Rosacea may also be treated with this invention.

Eczema is a form of inflammation of the skin which passes through several stages. Initially there is redness due to skin blood vessels dilating. Fluid accumulates in the skin causing swelling, itching and blistering. These may burst and become infected but eventually dry scabs and crusts may form. Therefore this condition results in lesions of the skin surface at affected sites, a manifestation not present in the skin disorders and irritations and inflammations described in the previous disclosures on therapeutic and prophylactic uses of zinc glycerolate. The five common types of eczema are contact, atopic, seborrhoeic, discoid and varicose. The site of the eczema varies with the type. The application of zinc glycerolate according to the present invention may be to one or more of these forms of eczema.

Hence in one form therefore the invention is said to reside in a method of treatment of a human or animal body comprising the step of application of a

pharmaceutically acceptable amount by oral, parenteral or topical application of zinc glycerolate for the treatment of skin diseases comprising acne and eczema for prophylactic or therapeutic treatment.

- 5 In a further form the invention is said to reside in the use of zinc glycerolate in a pharmaceutically acceptable amount by oral, parenteral or topical application for the for prophylactic or therapeutic treatment of skin diseases comprising acne and eczema as discussed above .

- 10 In a still further form the invention can be said to reside in zinc glycerolate when used as a pharmaceutical in a pharmaceutically acceptable amount by oral, parenteral or topical application the treatment of skin diseases comprising acne and eczema as discussed above for prophylactic or therapeutic treatment.

- 15 The unsuspected and surprising discovery is that the use of zinc glycerolate as a pharmaceutical appears to provide relief from the symptoms of these diseases and also appears to provide some alleviation of the underlying causes of these diseases.

- 20 Application of zinc glycerolate can be topical and can be applied as a dry powder or as a suspension in a suitable liquid medium such as a cream or semi-solid medium such as an ointment and can be applied topically by an applicator, for instance by transdermal delivery patch where internal mobilisation in the blood is required for transport to other internal remote areas or application can be by or a spray or puffer pack. Alternatively it can be applied by parenteral means such as by injection in a suitable suspension or solution. Oral intake in the form of a tablet, capsule or lozenge may also be suitable for some applications of the invention.

- 25 One suitable way of treatment might include application as a cream or ointment including in its formulation zinc glycerolate to the affected body part.

- 30 It is believed that the action of zinc glycerolate for treatment in the ways as discussed above relates to the ability of the compound to be easily adsorbed into the human or animal body and to release the zinc from within the compound in a form that is readily useable.

Hence unexpectedly it appears that the application of the zinc glycerolate has a beneficial effect in alleviating the symptoms of or treating a number of diseases.

The applicant's have carried out tests to determine the effectiveness of the glycerolate therapy on the conditions and diseases enumerated herein and

believe that the results achieved in showing the effectiveness of the compound for treatment of these are entirely unsuspected.

DESCRIPTION OF THE PREFERRED METHOD AND EXAMPLES

Acne Vulgaris

- 5 Patients were examined with treatment using zinc glycerolate in the form of a powder plus other treatments. Examination of patients was carried out every seven days.

Eight patients with Acne Vulgaris were investigated. zinc glycerolate was applied on trunk lesions simultaneously with general vitamin treatment. In four cases Tetracycline was administered as well as Netronidasole. The period of observation varied from two to four weeks. In three case improvement of dermatological status was observed. Another four patients did not show any improvement and local status of one patient worsened.

10 In another test zinc monoglycerolate in the form of a cream was applied to Acne Vulgaris. In two weeks there was a decrease of new eruptions of approximately 50%.

Acne Rosacea

Zinc monoglycerolate in the form of a cream was applied to Acne Rosacea and found to have an anti-inflammatory effect superior to hydrocortisone. It was found possible to use the cream including zinc glycerolate as a base under cosmetic make up.

Atopic eczema

A double blind placebo controlled evaluation of the efficacy and safety of zinc glycerolate in the form of a powder in the treatment of mild to moderate childhood atopic eczema was carried out. The placebo was BP Talc.

The results indicated that:

1. Zinc Glycerolate worked very well in the study as it showed improvements in Global Impression Scores, Global Change Scores, Area affected Mean Score, Total Symptoms Score and Total Eczema Score, these improvements being statistically significant each week over the four weeks of the trial.

2. The Global Change Score for Zinc Glycerolate was 86% improved at four weeks which was higher than the 65% assumed at the time of preparing the trial protocol.
3. It was noted that there was no discernible difference in the efficacy of the two treatments for patients who started with mild eczema (Total Eczema Scores less than 20), whereas there was an obvious difference in favour of Zinc Glycerolate with patients who started with moderate eczema.
4. Zinc Glycerolate was assessed favourably relative to the placebo by the patients in their diaries.

10 It is concluded that Zinc Glycerolate performed better than expected in the trial.

Further Test on Atopic eczema

An open pilot study of six patients (children aged from 2 to 10) was carried out using zinc glycerolate in the form of a powder. It was applied twice a day for two weeks to one side of the body and compared with the current emollient used by the patients applied on the other side of the body (this was Diprobase cream (Kirby Warwick) on all patients).

Parents were instructed to continue all the other anti-eczema treatments that they had been using such as topical steroid ointment, bath oil and anti-histamine medicine at night.

- 20 The results were that none of the patients reported any significant reduction in the inflammatory component of the eczema, comparing right with left. As an emollient or moisturizer opinion was equally divided with two reporting preference for zinc glycerolate, two reporting no difference and two reporting preference for the Diprobase. There was a definite advantage reported in that the zinc glycerolate remained on the skin longer and hence did not require such frequent applications.

In a further open pilot study ten children in the age range of from 3 to 14 with moderate to severe eczema were studied.

- 30 Zinc glycerolate in the form of a powder was applied twice daily to one limb (in all cases the right leg).

Patients were instructed not to use any emollient cream on that area but to continue all other treatments, including a topical steroid, bath oil and in some cases an anti-histamine medicine at night.

In eight out of the ten patients there was a definite improvement comparing the treated limb with the non-treated limb. Both parents and children were convinced that the powder had helped. Comments included: "soothing"; "it helped dry the eczema"; less itchy". Examination revealed that there was a
5 significant decrease in the inflammation (redness) of the treated limb.

Two children who had severe uncontrolled eczema showed no change using the powder.

The powder was well tolerated by all the children with no adverse effects.


CLAIMS

1. A method of treatment of a human or animal body comprising the step of application of a pharmaceutically acceptable amount by oral, parenteral or topical application of zinc glycerolate for the treatment of skin diseases for prophylactic or therapeutic treatment.
2. A method of treatment as in Claim 1 wherein the skin disorder is acne.
3. A method of treatment as in Claim 1 wherein the skin disorder is eczema.
4. A method of treatment as in Claim 1 wherein the application of zinc glycerolate is selected from the group of topical application, for instance as a dry powder, by suspension in a suitable liquid medium, for instance as a cream or ointment or applied topically by an applicator.
5. A method of treatment as in Claim 1 wherein the application of zinc glycerolate is parenteral means such as by injection in a suitable suspension or solution.
6. A method of treatment as in Claim 1 wherein the application of zinc glycerolate is in the form of a tablet, capsule or lozenge.
7. The use of zinc glycerolate in a pharmaceutically acceptable amount by oral, parenteral or topical application for the for prophylactic or therapeutic treatment of skin diseases.
8. Zinc glycerolate when used as a pharmaceutical in a pharmaceutically acceptable amount by oral, parenteral or topical application the treatment of skin diseases for prophylactic or therapeutic treatment.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 93/00354

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. ⁵ A61K 31/315 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC : A61K 31/315 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU : IPC as above Electronic data base consulted during the international search (name of data base, and where practicable, search terms used) WPAT JAPIO				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.		
X	AU,A, 62865/86 (GLYZINC PHARMACEUTICALS LIMITED) 12 March 1987 (12.03.87) whole document	1-8		
X	WO,A, 82/01867 (TAYLOR, Reginald Morton et al) 10 June 1982 (10.06.82) whole document	1-8		
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="display: flex; align-items: center;"> <input type="checkbox"/> Further documents are listed in the continuation of Box C. </div> <div style="display: flex; align-items: center;"> <input checked="" type="checkbox"/> See patent family annex. </div> </div>				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width: 50%; vertical-align: top;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle of theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle of theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 29 October 1993 (29.10.93) (0..93.)		Date of mailing of the international search report 5 NOV 1993 (5.11.93)		
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929		Authorized officer  J. P. PULVIRENTI Telephone No. (06) 2832261		

Information on patent family members

PCT/AU 93/00354

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
AU	62865/86	GB	2191941	JP	63500664	WO	87/01281
WO	82/01867	AU	78032/81	DE	3152555	FR	2494583
		GB	2101132	JP	57501783	JP	2056337
		US	4544761				